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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,037	09/17/2003	Richard D. Guarino	P-6186	2610

47656 7590 07/11/2007

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EXAMINER	
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ART UNIT	PAPER NUMBER
1657	

MAIL DATE	DELIVERY MODE
07/11/2007	PAPER

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/664,037
Filing Date: September 17, 2003
Appellant(s): GUARINO ET AL.

Guarino et al.

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 3/02/2007 appealing from the Office action mailed 10/04/2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows:

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner:

Rejection of claims 1-3, 7, 8, 12-15 and 62-64 under 35 U.S.C. 102(b) as being anticipated by WO 98/56897.

Rejection of claims 1-3, 7, 8, 14-16 and 62-64 under 35 U.S.C. 102(e) as being anticipated by US 6,562,616 (Toner et al).

Rejection of claims 1-3, 7, 8, 14, 15 and 61-64 under 35 U.S.C. 102(b) as being anticipated by US 5,942,436 (Dunn et al).

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

US 6,562,616	TONER et al.	5-2003
US 6,653,105	TRIGLIA et al.	11-2003
US 5,942,436	DUNN et al.	8-1999
WO 98/56897	ABATANGELO et al.	12-1998
JP 04322657	FUKUDA et al.	11-1992

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6-8, 10, 12-16, 58 and 61-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/56897, US 6,562,616 (Toner et al) and US 5,942,436 (Dunn et al) taken with US 6,653,105 (Triglia et al) and JP 04322657.

Claims are directed to a method for culturing primary liver cells wherein the method comprising (a) providing a polymer composition comprising a cell adhesion resistant (CAR) material, ECM protein(s) and a polycationic polymer in order to form a cell adhesion promoting surface; and (b) incubating the liver cells in the presence of the surface and a culture medium wherein the liver cells attach to the surface and are maintained in a functional state. Some clams are further dawn to the use of CAR material such as hyaluronic acid (HA). Some clams are further dawn to the use of ECM proteins such as collagen type I. Some clams are further dawn to the use of polycationic polymer such as of poly-ornithine. Some clams are further dawn to the use Some claims are further drawn to the use of 3D scaffold formed by ECM proteins and to the use of flexible material in the surface polymer composition such as PDMS. Some claims are further drawn to the use of rat liver cells or human liver cells.

The cited WO 98/56897, US 6,562,616 (Toner et al) and US 5,942,436 (Dunn et al) teach methods for culturing mammalian liver cells including rat and human liver cells attached to ECM proteins such as collagen type I that is coated on/bound to non-adhesive (CAR) materials including HA.

For example: see WO 98/56897 at page 13, example 6, wherein the patent discloses a method for attaching and maintaining primary porcine liver cells in a functional state by incubating the liver cells in a culture medium on a nonwoven HYAFF in co-culture with dermal fibroblasts that are seeded on the nonwoven HYAFF. The HYAFF matrices are made from hyaluronic acid (paragraph bridging pages 1 and 2). ECM proteins including collagen type I are provided by dermal fibroblasts. The dermal fibroblast ECM proteins provide for 3D scaffold for

liver cells and plastic 24-well dishes are made from flexible material within the broadest meaning of the claims.

US 6,562,616 (Toner et al) discloses a method for attaching and/or maintaining primary porcine liver cells (col. 24, lines 52-63) wherein the method comprising incubating the liver cells on collagen type I coated glass slides. Glass is a generic CAR material. The ECM proteins such as collagen type I provide liver cells for 3D scaffold within the meaning of the claims. US 6,562,616 also teaches the use of a polycationic polymer or PDMS polymer materials for forming the surface composition in the method for culturing liver cells. The liver cells are maintained in viable state (example 8) and, thus, they are in functional state including p450 activity and ability to secrete albumin that are inherent features of hepatocytes.

US 5,942,436 (Dunn et al) discloses a method for culturing primary liver cells such as rat hepatocytes (col. 5, line 38) and human hepatocytes (col. 8) in culture vessels coated with collagen type I (rat tail collagen) (col.6, lines 5-26). The liver cell culture is maintained in a generic plastic dish that is made from plastic or generic flexible material within the broadest meaning of the claims. Plastic is polymer that is a generic CAR material within the broadest meaning of the claims. The patent teaches that liver cells are maintained in functional state as suitable for replacing liver function in vivo (col.8, lines 19-25) and thus, they have p450 activity and ability to secrete albumin that are inherent features of functional hepatocytes.

Thus, the cited WO 98/56897, US 6,562,616 (Toner et al) and US 5,942,436 (Dunn et al) teach methods for culturing mammalian liver cells including rat and human liver cells attached to ECM proteins such as collagen type I that is coated on/bound to non-adhesive (CAR) materials including HA. The cited references WO 98/56897, US 6,562,616 (Toner et al) and US 5,942,436

(Dunn et al) are lacking particular disclosure about the use of polycationic polymer or poly-L-ornithine in the surface coating composition in the method for culturing liver cells.

However, US 6,653,105 (Triglia et al) teaches methods for culturing mammalian liver cells including human hepatocytes (col. 4, line 6) and suggests the use of attachment surfaces that are composed of poly-ornithine and collagen as suitable compositions for attachment, incubating and growing hepatocytes (col. 6, lines 5-24).

The cited JP 04322657 also teaches and/or suggests culturing liver cells in the presence of biologically active composition such as a mixture of materials selected from collagen, poly-L-ornithine, glasses, organic polymers and/or silicone-based rubbers (see English abstract).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to add poly-L-ornithine taught by US 6,653,105 (Triglia et al) and JP 04322657 to the coating polymer compositions of WO 98/56897, US 6,562,616 (Toner et al) and/or US 5,942,436 (Dunn et al) with a reasonable expectation of success in culturing liver cells because the cell attachment surfaces comprising poly-L-ornithine and collagen type I have been taught and/or suggested by the prior art of attaching, incubating and growing hepatocytes as adequately demonstrated by the cited reference combined. The CAR materials (cell adhesion resistant or non-adhesive) including HA have been known and used as a support material for cell-adhesive coating as adequately demonstrated by WO 98/56897, US 6,562,616 (Toner et al) and/or US 5,942,436 (Dunn et al). Thus, all cited references are in the same field of endeavor and seek to solve the same problems as the instant application and claims, and one of skill in the art is free to select components available in the prior art, *In re* Winslow, 151 USPQ 48 (CCPA, 1966).

Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary. The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

(10) Response to Argument

Applicant's arguments filed 3/02/2007 have been fully considered but they are not all found persuasive.

The claim rejections under 35 U.S.C. 102(b) as being anticipated by WO 98/56897 or by US 6,562,616 (Toner et al) or by US 5,942,436 (Dunn et al) have been withdrawn because the cited reference do not teach the use of "a polycationic polymer" within the materials of the culture vessels in methods for culturing mammalian liver cells.

With regard to the claim rejection under 35 USC § 103 applicants argue (appeal brief pages 7-11) that the cited WO 98/56897, US 6,562,616 (Toner et al) and/or US 5,942,436 (Dunn et al) are silent about the use of polyornithine as a polycationic polymer in the materials of the culture vessel and that the cited secondary references US 6,653,105 (Triglia et al) and JP 04322657 teach the use of polyornithine as an invitation for experimentation rather than a direct suggestion.

This argument is not found persuasive because US 6,653,105 (Triglia et al) and JP 04322657 clearly teach the use of polyornithine (a polycationic polymer) together with collagen as cell adhesion promoting materials in the list of materials suitable for attachment and maintenance of liver cells. The cited references are in the same field of endeavor and seek to

solve the same problems as the instant application and claims, and one of skill in the art is free to select components available in the prior art, *In re* Winslow, 151 USPQ 48 (CCPA, 1966).

Moreover, motivation can come not only from direct teaching of the prior art, but also the nature of the problem to be solved and/or the knowledge of persons of ordinary skill in the art, Ruiz v. A.B. Chance Co. 357 F.3d 1270, 69 USPQ2d 1686 (2004). The cited references are in the same field of endeavor and seek to solve the same problems as the instant application and claims, and one of skill in the art is free to select components available in the prior art, *In re* Winslow, 151 USPQ 48 (CCPA, 1966). Further, the examiner recognizes that references cannot be arbitrarily combined that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references, *In re* Nomiya, 184 USPQ 607 (CCPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. One test for combining references is what the combination of disclosures taken as a whole would suggest to one versed in the art, rather than by their specific disclosures, *In re* Bozek, 163 USPQ 545 (CCPA 1969).

In this case, all particular claimed components including HA, collagen type I and poly-L-ornithine are known in the art, and used for their known art specific properties, in different combination for culturing liver cells as adequately demonstrated by the cited references. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary. The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references.

Applicants' argument that one of the prior art reference such as US'105 teaches culturing of established liver cell lines rather than culturing primary liver cells is not found convincing

since the claimed method relates to culturing cells on cell adhesion promoting surfaces and because all cited references demonstrate the presently claimed materials have been known and used in the prior art of attaching, incubating and growing hepatocytes including primary liver cells as adequately demonstrated by the cited reference combined.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Therefore, the claims are properly rejected under 35 USC § 103.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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V. Afremova

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